

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068195 A1

- (51) International Patent Classification⁷: A61K 9/44 (74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).
- (21) International Application Number: PCT/GB03/00594
- (22) International Filing Date: 12 February 2003 (12.02.2003) (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0203296.9 12 February 2002 (12.02.2002) GB
0203297.7 12 February 2002 (12.02.2002) GB
0203298.5 12 February 2002 (12.02.2002) GB
- (71) Applicant (*for all designated States except US*): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): MARTINI, Luigi [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). RE, Vincenzo [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LI, Chi, Leung [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WILLY, Helen, Anne [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/068195 A1

(54) Title: ORAL DOSAGE FORM FOR CONTROLLED DRUG RELEASE

(57) Abstract: An oral dosage form comprising, (i) an erodable core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and (ii) an erodable coating surrounding said core, which coating comprises one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core; characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the dosage form occurs through the said opening(s) by the erosion of said erodable core and through erosion of said erodable coating under pre-determined pH conditions; a process for preparing such a dosage form and the use of such a dosage form in medicine.

ORAL DOSAGE FORM FOR CONTROLLED DRUG RELEASE

Field of the invention

5 The invention relates to an oral dosage form which provides controlled release of an active pharmaceutical agent in different body environments, to a process for preparing such a dosage form and to the use of such a dosage form in medicine.

Background to the invention

10 The use of a coating to control the rate of release of an active agent has received considerable attention and many different devices have been developed for such a purpose. For example, International Patent Application, Publication Number WO 01/05430 describes a drug delivery device that enables the delivery of drug substances which exhibit pH dependent solubility, in particular compounds that are more soluble at low pH levels (less than pH 2) than at near neutral levels (greater than about pH 5). Such
15 delivery devices are characterised by the presence of a coating that is impermeable and insoluble in the fluid of the environment of use.

International patent application, Publication Number WO 95/30422 describes a series of controlled-release dosage forms of azithromycin. In particular, there is
20 described a series of dosage forms that reduce the exposure of the upper GI tract (e.g. the stomach) to high concentrations of azithromycin, by the use of a pH dependent coating. Such dosage forms do not feature openings through which release of the drug substance may occur.

25 US Patent Number 6,099,859 describes a controlled release tablet for the delivery of an antihyperglycemic drug, which comprises an osmotically active drug-containing core and a semipermeable membrane, wherein the semipermeable membrane is permeable to the passage of water and biological fluids and is impermeable to the passage of the drug substance. The semipermeable membrane contains at least one
30 passageway for the release of the antihyperglycemic drug.

Additional devices that utilise a coating to control the rate of release of an active agent are discussed in US Patent Number 5,004,614. This patent describes a tablet core provided with an outer coating that is substantially impermeable to environmental fluid.
35 The said outer coating may be prepared from materials that are either insoluble or soluble in the environmental fluids. Where a soluble material is used, the coating is of sufficient thickness that the core is not exposed to environmental fluid before the desired duration of the controlled release of the active agent has passed. Through this

impermeable outer coating, one or more opening(s) has been created, so as to provide environmental fluids with an access route to the core. Therefore, upon ingestion of the coated tablet, gastro-intestinal fluid can enter the opening(s) and contact or penetrate the core, to release the active agent. The result is that the active agent is released in a controlled manner out of the opening(s) only. The preferred geometry is such that there is a circular hole on the top and bottom face of the coated tablet. The opening(s) in question have an area from about 10 to 60 percent of the face area of the coated tablet. The rate of drug release is found to be directly related to the diameter of the opening(s) and to the solubility of the matrix core and active agent, allowing the possibility for a variety of drug release profiles be it zero or first order release.

This invention is based on the finding that the substantially impermeable coatings of US 5,004,614 are not suitable for the controlled release of all active agents, especially pharmaceutically active weak bases or pharmaceutically acceptable salts and solvates thereof. Such active agents exhibit a marked pH dependent solubility, i.e. they are more soluble at around pH 2, associated with regions found in the stomach, compared to their solubility in the generally neutral conditions of the small intestine, around pH 7.

We have found that for administration of a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, where it is desirable that release of the active compound takes place in more than one pH environment, it is beneficial for the coating to be erodable or soluble in a pH dependent manner.

Summary of the invention

Accordingly, in its broadest aspect the present invention provides an oral dosage form comprising an erodable core which contains a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, the core having a coating with one or more openings leading to the core, characterised in that the coating is erodable under predetermined pH conditions.

The present invention further provides an oral dosage form comprising,
(i) an erodable core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and
(ii) an erodable coating around said core, which coating comprises one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core;
characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the erodable core occurs

substantially through the said opening(s) and through erosion of said erodable coating under pre-determined pH conditions.

For the avoidance of doubt, as used herein the term "weak base" shall mean any base the conjugate acid of which has a pKa of less than 11.5; in accordance with *The Pharmaceutical Handbook*, 19th Edition, 1980. The term "pharmaceutically acceptable weak base" shall be interpreted accordingly. Suitably, pharmaceutically acceptable weak bases or pharmaceutically acceptable salts or solvates thereof for use in the present invention exhibit a marked pH dependent solubility. Preferably, pharmaceutically acceptable weak bases or pharmaceutically acceptable salts or solvates thereof for use in the present invention are more soluble in the pH range from 1 to 3 compared to their solubility in the pH range from 4.5 to 8. Preferred pharmaceutically acceptable weak bases or pharmaceutically acceptable salts or solvates thereof for use in the present invention are more soluble in the acidic conditions found in the mammalian stomach than in the near neutral conditions of the mammalian intestines.

Suitable pharmaceutically active weak bases for use in the present invention include – 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone ("bupropion"), 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one ("ondansetron"), (3*S-trans*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ("paroxetine"), α^1 -[[1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol ("salbutamol") and pharmaceutically acceptable salts and/or solvates thereof.

European Patent Application, Publication Number 0 306 228 A1 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0 306 228 A1 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound A'). International Patent Application, Publication Number WO 94/05659 discloses certain salts of Compound A including the maleate salt at Example 1 thereof.

Compound A and pharmaceutically acceptable salts or solvates thereof have useful pharmaceutical properties. In particular Compound A or a salt or solvate thereof is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

A preferred pharmaceutically active weak base for use in the present invention is Compound A or a pharmaceutically acceptable salt or solvate thereof. A particularly preferred pharmaceutically active weak base for use in the present invention is the maleate salt of Compound A.

5

A further preferred pharmaceutically active weak base for use in the present invention is valaciclovir or a pharmaceutically acceptable salt thereof. Valaciclovir is the L-valine ester of acyclovir and is named 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl L-valinate. A preferred salt of this compound is the hydrochloride salt, known as valaciclovir hydrochloride. Valaciclovir and the hydrochloride salt thereof are disclosed in US Patent Number. 4,957,924 (see particularly Example IB), European Patent Number EP 0 308 065 B1 (see particularly Example IB), and L.M. Beauchamp et al, *Antiviral Chemistry and Chemotherapy*, 3(3), 157-164 (1992) (see particularly page 162 column 1), all of which are incorporated herein by reference as though fully set forth. A preferred anhydrous crystalline form of valaciclovir hydrochloride is disclosed in International Patent Application, Publication Number WO 96/22291 (incorporated herein by reference as though fully set forth); this anhydrous crystalline form can for example be defined by having substantially the X-ray powder diffraction pattern of one or more of Figures 1 to 3 of WO 96/22291. Some syntheses of valaciclovir and its hydrochloride salt are given in WO 96/22291, e.g. see Examples 1A/B and 2A/B and pages 4-7 therein.

Valaciclovir or a salt thereof can be used in the treatment and/or suppression of a viral infection in a mammal such as a human, particularly a viral infection caused by the herpes group of viruses, e.g. herpes zoster and/or herpes simplex virus types 1 or 2. The following dosage regimes, wherein the doses are calculated as the valaciclovir free base, are given for guidance:

- (a) treatment of episodes of herpes simplex virus types 1 and 2 infection:- total daily dose of about 1 or 2 g administered at 500 mg twice a day or 1 g twice a day for 5 to 10 days;
- (b) suppression of recurrences of herpes simplex virus types 1 and 2 infections (e.g. genital herpes):- total daily dose about 250 to 1 g (e.g. 500 mg twice a day) for about one month to ten years, depending on the patient. As disclosed in WO 97/25989 (incorporated herein by reference), valaciclovir or a salt thereof can also be used in the suppression of recurrent genital herpes in a human at a once daily dose of from about 200 mg to about 1000 mg (e.g. 250 mg, 500 mg or 1000 mg) valaciclovir or a salt thereof (calculated as the free base) for an effective treatment period e.g. for ca. 2 months up to ca. 10 years.

(c) treatment of varicella zoster virus infections (herpes zoster, e.g. shingles):- total daily dose about 3 g administered at 1 g three times a day for 7 days;

- (d) suppression of cytomegalovirus infections:- total daily dose about 8 g administered at 2 g 4 times a day; for transplant patients this daily dose is administered for three to six months for the period at risk; and for HIV positive patients a daily dose is administered as usually indicated for improving quality of life, for example for two years or more.

Suitably, the pharmaceutically acceptable weak base is selected from the group consisting of 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone ("bupropion"), 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one ("ondansetron") and (3*S-trans*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ("paroxetine"), 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl L-valinate ("valaciclovir"), Compound A and pharmaceutically acceptable salts and/or solvates thereof (hereafter "the Primary Compounds of the invention"). Suitably, the pharmaceutically acceptable weak base is 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone ("bupropion") or a pharmaceutically acceptable salt or solvate thereof. Suitably, the pharmaceutically acceptable weak base is 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one ("ondansetron") or a pharmaceutically acceptable salt or solvate thereof. Suitably, the pharmaceutically acceptable weak base is (3*S-trans*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ("paroxetine") or a pharmaceutically acceptable salt or solvate thereof. More suitably, the pharmaceutically acceptable weak base is 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl L-valinate ("valaciclovir"). Most suitably, the pharmaceutically acceptable weak base is Compound A or a pharmaceutically acceptable salt or solvate thereof.

Brief description of the drawings

Figure 1 is a graph of dissolution against time for two formulations of oral dosage form in accordance with this invention.

Detailed description of the invention

Typical pharmaceutically active weak bases for use in the present invention are the Primary Compounds of the invention, in particular Compound A or a pharmaceutically acceptable salt or solvate thereof. Such compounds and pharmaceutically acceptable salts thereof exhibit a marked pH dependent solubility, i.e. they are more soluble at around pH 2, associated with regions found in the stomach,

compared to their solubility in the generally neutral conditions of the small intestine, around pH 7.

5 The Primary Compounds of the invention and pharmaceutically acceptable salts and solvates thereof have useful pharmaceutical properties which are well documented (e.g. the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press)).

10 The oral dosage form of this invention may be also be used to administer other pharmaceutically active weak bases with similar dissolution properties to the Primary Compounds of the invention, to treat disorders for which the weak base is known to be indicated.

15 The above reference to the coating being erodable includes the situation where the coating disintegrates partially or wholly, or dissolves, or becomes porous, on contact with an environmental fluid so as to allow the fluid to contact the core. Suitably the coating disintegrates partially. Suitably the coating disintegrates wholly. Suitably the coating dissolves. Suitably the coating becomes porous.

20 Similarly the references to the core being erodable includes the situation where core disintegrates partially or wholly, or dissolves, or becomes porous, on contact with an environmental fluid so as to allow the fluid to contact the active agent. Suitably the core disintegrates partially. Suitably the core disintegrates wholly. Suitably the core
25 dissolves. Suitably the core becomes porous.

30 While this invention provides that erosion of the coating is pH-dependent, the core may release the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof by eroding in a non-pH dependent manner. However to suit a specific demand, the core may be a material which allows pH dependent erosion or disintegration of the core to release the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from its matrix.

35 Most suitably, although the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof is more soluble in the stomach than the intestines, the core is formulated so as to be erodable to substantially the same extent under both conditions.

So that the opening(s) in the coating retains its integrity and control of release rate, it is desirable that the pH dependent erosion of the coating has a defined threshold, i.e. the coating does not substantially erode except in the intestines. Thus, it is envisaged that erosion of the coating has a defined, pre-determined pH threshold at which it
5 dissolves. Preferably, the coating erodes at pH > 4.5. More preferably, the coating erodes in the pH range from 4.5 to 8. Most preferably, the coating erodes in the pH range 5 to 7.

The present invention finds particular use in the situation where the coating
10 erodes in the pH conditions of the intestines. Accordingly, the present invention also provides an oral dosage form comprising an erodable core which contains a pharmaceutically active weak base or a pharmaceutically acceptable salt thereof, the core having a coating with one or more openings leading to the core, characterised in that the coating is erodable under the pH conditions prevailing in a mammalian intestine.

15 It will be appreciated that the use of a coating that erodes at pH > 4.5 will restrict the amount of drug released into the acidic conditions associated with the stomach, since release is at low pH levels is substantially limited to diffusion of the active agent through the opening(s) in the erodable coating. Thus, the present invention is indicated to
20 address the problem of "dose dumping" in the stomach for compounds that are more soluble in the pH range from 1 to 3 than in the pH range from 4.5 to 8. As the dosage form leaves a low pH environment and then encounters a higher environmental pH, e.g. moves from the stomach into the intestine, the coating will start to dissolve and erode away to expose all of the tablet core. During coat erosion, the available surface area to
25 release drug is increased. The decrease in drug solubility and therefore rate of drug adsorption in the intestine can be compensated for by the increase in the surface area due to all the faces of the tablet core being exposed to erosion. The result is a more balanced drug release profile in both environments.

30 In applying the concepts of this invention, the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof may be incorporated into a conventional oral tablet or controlled release matrix (including both swellable and non-swellable systems). The matrix is formed into cores which are then coated with a material with pH-dependent erodability, for example a coating soluble at pH > 4.5, such
35 as a polymethacrylate copolymer. One or more openings may then be drilled through the coatings using conventional techniques as disclosed in US 5,004,614.

According to a further aspect of the present invention, there is provided a process for the preparation of an oral dosage form according to the present invention, which process comprises:

- (a) preparing an erodable tablet core;
- 5 (b) coating the core with a material with pH-dependent erodability; and
- (c) creating one or more openings in the coating, said opening(s) extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core.

10 The core may be prepared by compressing suitable ingredients to form a compacted mass which comprises the core of the dosage form (also referred to herein as "tablet core"). This may be prepared using conventional tablet excipients and formulation compression methods. Thus, the core typically comprises the active agent or agents along with excipients that impart satisfactory processing and compression
15 characteristics such as diluents, binders and lubricants. Additional excipients that may form part of the core of the device include disintegrants, flavourants, colorants, release modifying agents and/or solubilising agents such as surfactants, pH modifiers and complexation vehicles.

20 Suitable materials for the core include erodable polymethylmethacrylate resins such as the Eudragit™ series, for example Eudragit™ L30D, saccharoses, for example lactose and maltose, and cellulose esters, for example methylcellulose, hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose. Suitably, the core is predominantly hydroxypropylmethylcellulose and lactose. More suitably, the core
25 consists essentially of hydroxypropylmethylcellulose, lactose, colloidal silicon dioxide and magnesium stearate.

Typically the active agent and excipients are thoroughly mixed prior to compression into a solid core. The core of the device may be formed by wet granulation
30 methods, dry granulation methods or by direct compression. The core may be produced according to any desired pre-selected shape such as bi-convex, hemi-spherical, near hemi-spherical, round, oval, generally ellipsoidal, oblong, generally cylindrical or polyhedral, e.g. a triangular prism shape. The term "near hemi-spherical" is intended to be construed in the manner described in US 5,004,614. Suitably the core is formulated
35 into a bi-convex shape, e.g. having two domed opposite surfaces. In addition, the core may be produced in a multi-layered (e.g. bi- or tri- layered) form.

The quantity of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof present within the core is a matter to be determined based upon typical pharmaceutical considerations, e.g. known dosages for the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, and is not limited by the process of this invention.

In particular, where Compound A or a pharmaceutically salt or solvate thereof is used in accordance with the present invention, a suitable dosage range is 2 to 12 mg. Thus, suitable dosage forms comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 2 to 4 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 4 to 8 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 8 to 12 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

One dosage form comprises 2 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Preferred dosage forms comprise 4 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Preferred dosage forms comprise 8 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

The core may be coated with a suitable pH dependent erodable material by any pharmaceutically acceptable coating method. Examples include coating methods disclosed in US 5,004,614 and film coating, sugar coating, spray coating, dip coating, compression coating, electrostatic coating. Typical methods include spraying the coating onto the tablet core in a rotating pan coater or in a fluidised bed coater until the desired coating thickness is achieved. Suitably the coating is provided to add about 4 to 8 mg/cm² or 5 - 7 mg/cm² of dry polymer around the tablet surface area. Typically this results in an increase in weight (relative to the core) of from 3 - 10% or 5 - 10 % by weight. Suitably, the coating has a thickness in the range 0.05 to 0.5 mm.

Materials and their blends suitable for use as a pH-dependent erodable coating material in this invention include various polymethacrylate polymers, coprocessed polyvinylacetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, shellac, hydroxypropylmethylcellulose phthalate polymers and their copolymers.

The coating material is suitably selected so that it is insoluble in stomach acid i.e. at pH 1.5 – 2, and is soluble or erodable in the small intestine i.e. at around pH 5.5 or in the large intestine i.e. at around pH 7. To achieve this, typically the material of the coating is erodable at pH of 4.5 or above.

5

Suitably, the coating material is selected from:
cellulose acetate trimellitate (CAT) dissolving @ pH 4.8,
polyvinyl acetate phthalate dissolving @ pH 5.0,
hydroxypropylmethylcellulose phthalate 50 dissolving @ pH 5.2,
10 hydroxypropylmethylcellulose phthalate 55 dissolving @ pH 5.4,
Acryl-eze™ dissolving @ pH 5.5,
Aquateric™ dissolving @ pH 5.8,
cellulose acetate phthalate dissolving @ pH 6.0,
Eudragit™ L30 D dissolving @ pH 5.5,
15 Eudragit™ L dissolving @ pH 6.0,
Eudragit™ S dissolving @ pH 6.8, and
shellac dissolving @ pH 7.2.

When necessary, the erodable coating may be modified by addition of plasticisers
20 or anti-tack agents. Suitable materials for this purpose include waxy materials such as
glycerides, for example glyceryl monostearate.

Typical sizes for the opening(s), when circular, to be formed in the coating are in
the range 0.5 mm – 8 mm of diameter, such as 1, 2, 4 or 4 mms in diameter, depending
25 on the overall size of the tablet and the desired rate of release. The opening(s) may have
any convenient geometrical shape, but a rounded shape, e.g. substantially circular or
elliptical, is generally preferred. More elaborate shapes, such as text characters or
graphics, may also be formed, provided that the release rate can be made uniform in
individual dosage forms. Typical sizes of non-circular openings are equivalent in area to
30 the above mentioned sizes for circular openings, thus in the range of from about 0.19 to
about 50.3 mm².

For the purposes of the present invention, the term "opening" is synonymous with
hole, aperture, orifice, passageway, outlet etc.

35

The opening(s) may be formed by methods disclosed in US 5,004,614. Typically
opening(s) may be formed by drilling, for example using mechanical drill bits or laser
beams, or by punches that remove the cut area. The formation of the opening(s) may by

default remove a small portion of the exposed core. It is also possible to purposely form a cavity below the aperture as a release rate controlling device, the cavity exposing a greater initial surface area of core than a flat surface. Suitably, the opening(s) extend through the entire erodable coating such that there is immediate exposure of the core to the environmental fluid when the device is placed in the desired environment of use.

Also it is possible to form the opening(s) *in situ* when the dosage form is administered, by forming a coating containing pore-forming agents i.e. material that will dissolve in the stomach to create pores in the coating. Accordingly, there is also provided an oral dosage form comprising,

- (i) an erodable core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and
- (ii) an erodable coating surrounding said core, which coating comprises a pore forming agent that is erodable in the pH range from 1 to 3 to form one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core; characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the dosage form occurs through the said opening(s) by the erosion of said erodable core and through erosion of said erodable coating under pre-determined pH conditions.

In US 5,004,614, the opening(s) preferably comprise about 10 - 60 % of the total face area of the tablet i.e. the upper and lower surfaces of a biconvex tablet. In the present invention, the opening(s) may comprise 0.25 to 70%, such as 10 - 70% of the total face area.

Alternatively, it may be useful to characterise the rate controlling effect of the opening(s) by reference to the area of the opening(s) relative to the total surface area of the coated tablet. Additionally, especially in cases where the core erodes by undercutting of the edges of the opening(s), the rate controlling effect may be related to the total circumference of the opening(s).

An unexpected finding is that two openings, for example one on each primary surface of a biconvex tablet, release an active agent from the core at a rate marginally greater than that of a single opening of the same overall area. However the variability of the release rate from the two openings is less than the variability of release rate from the corresponding single opening. Therefore, in the preferred embodiment of the invention, the coating of the core is provided with two, or more than two, apertures leading to the

core. More preferably, the erodable coating surrounding the core is provided with two, or more than two, openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core.

5 Where more than one opening is provided, the openings may be located on the same face of the oral dosage form, or on different faces. Suitably, the oral dosage form has two openings, one on each opposing face. Suitably, the oral dosage form is a tablet having two opposed primary surfaces, each surface having one opening through the coating.

10

 As a protection for the core material, to prevent contamination via the opening(s) before dosing, it may be desirable to provide a conventional seal coating to either the core, or to the dosage form after formation of the opening(s). The seal coat may be a sub-coat or over-coat to the erodable coating.

15

 By adjustment of the above variables and the surface area of the exposed core, the release rates in the different environmental conditions can be harmonised to obtain comparable release rates under different body environments, and so achieve more constant dosing to a patient.

20

 Preferably the dissolution rates of the oral dosage forms of this invention are arranged, for example by routine adjustment of the erodable coating and dimensions of the opening(s), so that the rate of release is substantially uniform in the different pH environments experienced by the dosage form on administration. Dissolution rates may be assessed by *in vitro* testing in solutions of the appropriate pHs. For example, when comparing dissolution in the stomach and intestine, tests may be carried out initially at pH 1.5 with a transfer to pH 6.8 after 2 hours or 4 hours, as an assumed time for residence in the stomach before emptying into the intestines of a notional patient in respectively fasted and fed conditions.

30

 The present invention further provides a method for the treatment and/or prophylaxis of disorders in a human or non-human mammal susceptible to treatment by a pharmaceutically acceptable weak base, which comprises administering an oral dosage form of this invention comprising a pharmaceutically acceptable weak base or a pharmaceutically acceptable salt or solvate thereof to a human or non-human mammal in need thereof.

35

In a preferred embodiment the present invention provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, which method comprises administering an oral dosage form of this invention comprising Compound A or a pharmaceutically acceptable salt or solvate thereof, to a human or non-human mammal in need thereof.

As used herein the term "pharmaceutically acceptable" embraces compounds, compositions and ingredients for both human and veterinary use. For example the term "pharmaceutically acceptable salt" embraces a veterinarily acceptable salt. In particular, suitable pharmaceutically acceptable salted forms of Compound A include those described in European Patent Number 0 306 228 and International Patent Application, Publication Number WO94/05659.

Suitable pharmaceutically acceptable solvates include hydrates.

No adverse toxicological effects are indicated in the above mentioned treatments.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

In the following Examples, tablet cores were formed by conventional means by mixing together the active ingredients with excipients and compressing to form the tablet core. These Examples are intended to be by way of illustration rather than limitation of the present invention, and Compound A is used simply as one example of a weak base suitable for use with the present invention.

Example 1

A core was formed from the following formulation:

	%w/w
Compound A (as maleate salt)	7.1
HPMC	30.0
Lactose	60.9
Colloidal silicon dioxide	0.5
Magnesium stearate	1.5

by compression to form 7 mm normal concave tablets of 150 mg.

The tablet cores were coated with a polymethacrylate resin soluble at pH 5.5 to a total weight of 160 mg.

- 5 An opening of diameter 3.0 mm was drilled through the coating in each of the two primary surfaces of the coated cores to expose the surface of the core.

Example 2

A core was formed from the following formulation:

10		%w/w
	Compound A (as maleate salt)	7.1
	HPMC	20.0
	Lactose	70.9
	Colloidal silicon dioxide	0.5
15	Magnesium stearate	1.5

by compression to form 7 mm normal concave tablets of 150 mg.

- 20 The tablet cores were coated with a polymethacrylate resin soluble at pH 5.5 to a total weight of 160 mg.

An opening of diameter 3.5 mm was drilled through the coating in each of the two primary surfaces of the coated cores to expose the surface of the core.

- 25 Due to the larger openings and lower HPMC content, the dosage forms of Example 2 exhibited a faster release of Compound A at pH 1.5 and pH 6.8.

30

35

Dissolution Tests

Figure 1 shows dissolution rates for the formulations of Examples 1 and 2 starting at pH 1.5 with a transfer to pH 6.8 after 4 hours, as an assumed time for residence in the fed stomach before emptying into the intestines. The medium for this dissolution test is initially an aqueous solution of sodium chloride and hydrochloric acid, pH 1.5 to mimic the pH found in the stomach environment. This medium is then titrated to pH 6.8 by the addition of aqueous sodium dodecyl sulfate and an aqueous solution of sodium acetate and tris(hydroxymethyl)methylamine after 4 hours to mimic the pH found in the intestine. Figure 1 shows that with an erodable coat, the release is substantially complete i.e. over 90% release is achieved, after about 8 hours for the formulation of Example 2, and 12 hours for the formulation of Example 1. During that period, the rate of release is substantially uniform at both pHs, for both formulations.

Testing in the same solutions with transfer at 2 hours to mimic gastric emptying in the fasted condition, gave similar results.

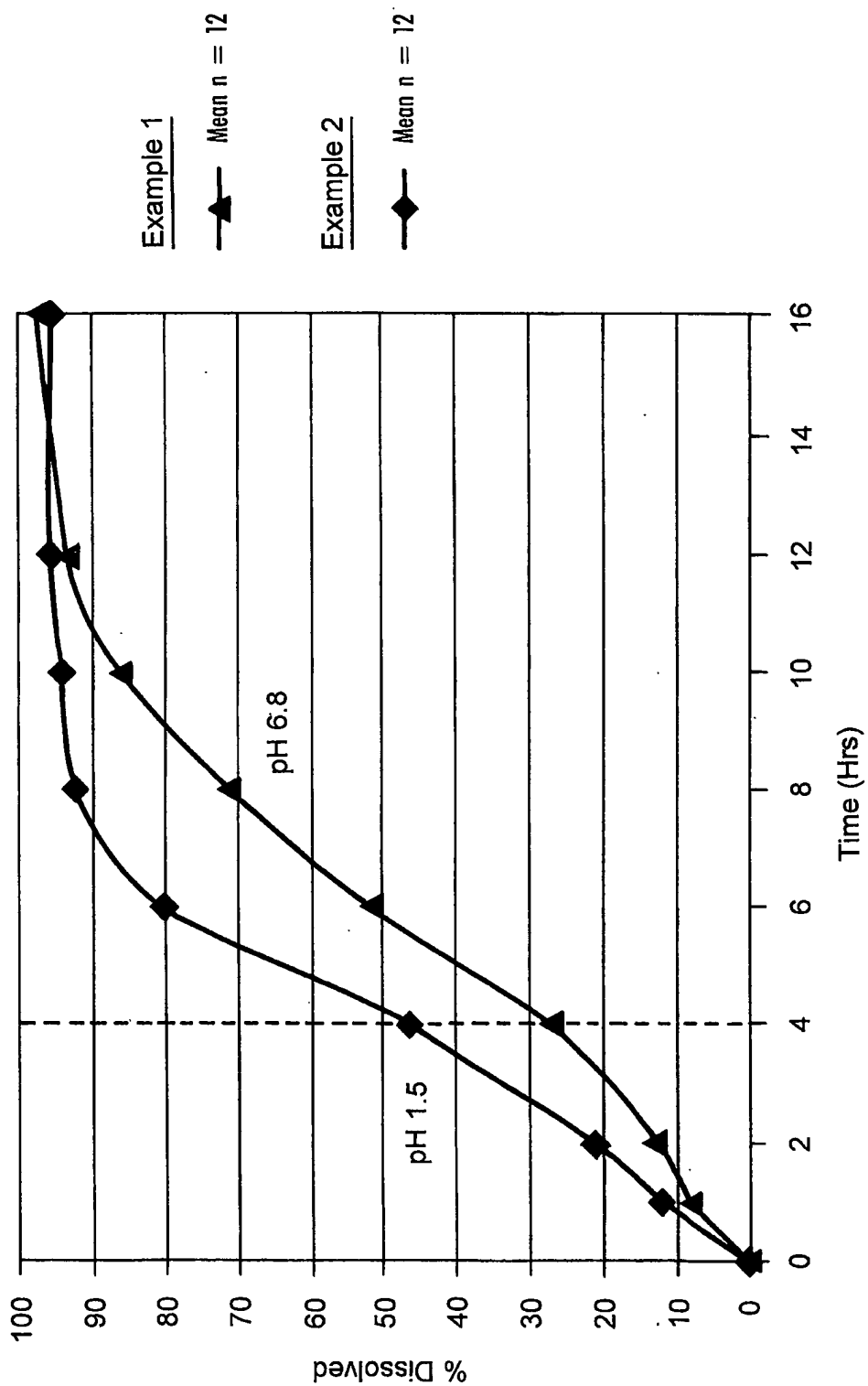
Claims

1. An oral dosage form comprising,
 - 5 (i) an erodable core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and
 - (ii) an erodable coating around said core, which coating comprises one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core;
- 10 characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the dosage form occurs through the said opening(s) by the erosion of said erodable core and through erosion of said erodable coating under pre-determined pH conditions.
- 15 2. An oral dosage form according to claim 1 in which the erodable coating erodes at pH > 4.5.
3. An oral dosage form according to claim 1 in which the erodable coating material is selected from polymethacrylate polymers, coprocessed polyvinylacetate phthalate,
20 cellulose acetate trimellitate, cellulose acetate phthalate, shellac, hydroxypropyl-methylcellulose phthalate polymers and their copolymers, and blends thereof.
4. An oral dosage form according to any preceding claim in which the erodable coating has a thickness in the range 0.05 to 0.5 mm.
- 25 5. An oral dosage form according to any preceding claim in which the opening(s) sizes are in the range 0.5 mm to 8 mm.
6. An oral dosage form according to any preceding claim in which the erodable
30 coating comprises two openings.
7. An oral dosage form according to any preceding claim, in which the erodable core is in a multi-layered form.
- 35 8. An oral dosage form according to any preceding claim in which the opening(s) in the erodable coating comprise about 10 to 70 % of the total face area of the dosage form.

9. An oral dosage form according to any preceding claim in which the core is predominantly hydroxypropylmethyl cellulose and lactose.
10. An oral dosage form according to any preceding claim in which the
5 pharmaceutically acceptable weak base is selected from the Primary Compounds of the invention or a pharmaceutically acceptable salt or solvate thereof.
11. An oral dosage form according to claim 10, in which the pharmaceutically acceptable weak base is 5-[4-[2-(N-methyl-N-(2-
10 pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione ('Compound A') or a pharmaceutically acceptable salt or solvate thereof.
12. A process for the preparation of an oral dosage form according to claim 1, which process comprises:
15 (a) preparing an erodable tablet core;
(b) coating the core with a material with pH-dependent erodability; and
(c) creating one or more openings in the coating, said opening(s) extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core.
20
13. A method for the treatment and/or prophylaxis of disorders in a human or non-human mammal susceptible to treatment by a pharmaceutically acceptable weak base, which comprises administering an oral dosage form according to claim 1 comprising a pharmaceutically acceptable weak base or a pharmaceutically acceptable
25 salt or solvate thereof to a human or non-human mammal in need thereof.

1/1

Fig. 1



INTERNATIONAL SEARCH REPORT

Internat application No
PCT/GB 03/00594

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 01925 A (FORUM CHEMICALS LIMITED) 8 March 1990 (1990-03-08) page 1, line 1 - line 6 page 17, line 2 - line 12 & US 5 004 614 A 2 April 1991 (1991-04-02) -----	1-13
P,X	WO 02 38131 A (SMITHKLINE BEECHAM P.L.C.) 16 May 2002 (2002-05-16)	12
P,A	page 1, line 1 - page 6, line 15 page 3, line 27 - line 33 -----	1-11,13
A	GB 2 150 830 A (ALZA CORPORATION) 10 July 1985 (1985-07-10) page 4, column 2, line 75 - column 2, line 118 claims 1,6,8 -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the International search

16 June 2003

Date of mailing of the International search report

25/06/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/00594

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat application No
PCT/GB 03/00594

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9001925 A	08-03-1990	AT 110262 T AU 4218489 A CA 1339079 A1 DE 68917677 D1 DE 68917677 T2 EP 0365123 A1 ES 2058543 T3 WO 9001925 A1 GB 2222948 A ,B IE 63764 B1 US 5004614 A	15-09-1994 23-03-1990 29-07-1997 29-09-1994 22-12-1994 25-04-1990 01-11-1994 08-03-1990 28-03-1990 14-06-1995 02-04-1991
WO 0238131 A	16-05-2002	AU 1828002 A WO 0238131 A2	21-05-2002 16-05-2002
GB 2150830 A	10-07-1985	AU 566109 B2 AU 2235483 A CA 1231283 A1 CH 659584 A5 DE 3400496 A1 FR 2560044 A1 JP 1894450 C JP 6023090 B JP 60174713 A	08-10-1987 20-06-1985 12-01-1988 13-02-1987 18-07-1985 30-08-1985 26-12-1994 30-03-1994 09-09-1985